Facilitation of the Lesioned Motor Cortex During Tonic Contraction of the Unaffected Limb Corresponds to Motor Status After Stroke

Shin-Yi Chiou, PT, PhD, Ray-Yau Wang, PT, PhD, Kwong-Kum Liao, MD, and Yea-Ru Yang, PT, PhD

Background and Purpose: Contraction of the muscles of the unaffected hand is associated with enhanced activation of lesioned motor cortex (ie, crossed facilitation) in some individuals after stroke. However, the association between crossed facilitation and motor function status remains unclear. We investigated whether existence of crossed facilitation corresponds to motor status of the affected upper limb after stroke.

Methods: Data were collected from 58 participants with unilateral stroke. The Fugl-Meyer assessment of upper extremity (FMA-UE) was used to evaluate motor status. Motor-evoked potentials (MEPs) were elicited from the abductor pollicis brevis (ABP) of the affected side under 3 conditions: rest, tonic contraction of the ABP of the unaffected side, or tonic contraction of the tibialis anterior of the unaffected side.

Results: In 28 of the 58 participants, MEPs could be elicited from the affected ABP at rest; these participants also exhibited crossed facilitation during contraction on the unaffected side. Participants with MEPs at rest exhibited higher FMA-UE scores (53.04 ± 2.59) compared with participants with absent MEP (19.83 ± 1.60; Z = −6.21). Seven participants with no MEPs at rest had MEPs with crossed facilitation; their FMA-UE scores were higher compared with the 23 who had no ABP MEP under any condition (Z = −2.66). FMA-UE scores were positively correlated with the amount of crossed facilitation during the APB task (r = 0.68) and the tibialis anterior task (r = 0.54).

Discussion and Conclusions: In some participants, MEPs in the affected hand muscle were enhanced by tonic contraction of the muscles on the unaffected side even if no MEP could be evoked at rest. The degree of crossed facilitation in the affected hand muscle was correlated with the level of motor function of the affected upper limb, and the FMA-UE score could classify the presence/absence of crossed facilitation.

Video abstract available for more insights from the authors (Supplemental Digital Content 1, http://links.lww.com/JNPT/A117).

Key words: ipsilateral muscle contraction, motor cortex lesion, motor status, stroke, transcranial magnetic stimulation

INTRODUCTION

Balanced interhemispheric interaction is required for motor performance of both unimanual and bimanual tasks. A unilateral cerebral lesion can interrupt the balance between damaged and undamaged cortices, resulting in an increase in interhemispheric inhibition from the unaffected to the affected motor cortex. The corticospinal tract arising from the cortical motor areas (eg, primary motor cortex [M1], premotor areas) is a major descending motor pathway controlling voluntary motor function with prominent interactions between both hemispheres. In healthy humans, it is well established that corticospinal excitability in the resting arm muscles is increased by isometric contractions of the contralateral arm muscles. This “crossed facilitation” has been suggested to contribute to interlimb coordination during unimanual and bimanual actions as well as to improvement in motor performance after repeated training.

It is evident that crossed facilitation is impaired after a stroke. For instance, corticospinal excitability to the affected hand muscle was found not to be correlated with the levels of contraction strength performed by the unaffected hand in participants with stroke, whereas they were highly correlated in healthy subjects. Remner et al showed abnormal increases in corticospinal excitability to the affected hand during a bimanual task, suggesting an association between impaired crossed facilitation and abnormal interlimb coordination after a stroke. It has been shown that the recovery of upper limb function is related to the structural reserve and excitability of the corticospinal pathway and the interhemispheric balancing in both those acute and subacute stroke.

The current study investigated the association between crossed facilitation induced by the unaffected limb and motor function of the upper limb, as measured by the Fugl-Meyer.
assessment of upper extremity (FMA-UE), in individuals poststroke. Given that changes in corticospinal excitability, intracortical inhibition, and interhemispheric inhibition contribute to the control of crossed corticospinal facilitation in healthy subjects, we hypothesized that crossed facilitation in the affected hand muscle would be correlated with motor function of the upper limb after a stroke.

METHODS

Participants

Fifty-eight participants with stroke (mean age, 59.11 ± 12.45 years; 74% male and 57% ischemic) participated in the study. All participants had a chronic (>6 months; mean onset duration, 2.63 ± 1.89 years) unilateral hemispheric stroke with diagnosis of either ischemic or hemorrhagic type. Participants who had a history of stroke or who had any contraindications for transcranial magnetic stimulation (TMS), including metal implants, cardiac pacemaker, history of epilepsy, previous brain injury, neurosurgery, actively taking antidepressant, or other neuromodulatory drugs, were excluded.\(^1\),\(^2\) The study was performed in accordance with the Declaration of Helsinki. All subjects gave their written informed consent to the experimental procedures, which were approved by the Institutional Review Board of Taipei Veterans General Hospital. Participants were recruited in the Department of Physical Therapy of Taipei Veterans General Hospital. All participants completed all aspects of the protocol.

Experimental Procedure

The FMA-UE was used to assess the severity of the motor impairment in the upper limb and was conducted by a trained physical therapist (S.Y.C). The FMA is a performance-based quantitative measure for the assessment of impairments in clinics and has been shown to have a high interrater and intrarater reliability in individuals with stroke.\(^1\),\(^2\) The items assess movements from the proximal to distal parts of the upper extremity and the coordination of the joints of the upper extremity on a 3-point ordinal scale (0 = cannot perform; 1 = can perform partially; 2 = can perform fully). The section on the motor function of the upper limb consists of 33 items, and the maximum score is 66 points.

To assess motor-evoked potential (MEP) amplitude, participants were seated in a reclining chair with the torso and head supported. The experiment comprised 3 conditions: rest, active tonic contraction of the abductor pollicis brevis (ABP) of the unaffected side, or active tonic contraction of the tibialis anterior (TA) of the unaffected side (ie, the task muscles). In the rest condition, participants were asked to relax and fixate on a visual target directly in front of them. In the active conditions, participants were instructed to perform a tonic contraction using the task muscles of the unaffected limb while maintaining the other muscles at rest. The target muscle was the ABP on the affected hand (a-ABP). Participants were encouraged to perform 3 maximal isometric contractions (duration of 3-5 s) of either thumb abduction (APB task) or ankle dorsiflexion (TA task) against the resistance applied by the examiner (S.Y.C). The electromyography (EMG) obtained from the task muscles was rectified and calculated as the mean maximal EMG amplitude of at least 50 µV in at least 3 of 5 consecutive trials. The target contraction strength of the task was set at 75% of the mean maximal EMG, as crossed facilitation occurs prominently at higher contraction strength.\(^3\),\(^4\) The EMG of the target and task muscles was displayed on the screen to provide feedback to both the participant and the experimenter. The 2 active conditions were applied in a randomized order following the rest condition.

Transcranial magnetic stimuli were applied to the optimal scalp position for activation of a-APB at rest and during the 2 active conditions (APB task and TA task). In the active conditions, TMS was delivered when the rectified EMG signal in the target muscle reached 75% of the mean maximal EMG activity; a minimum 5-second rest interval was interposed between each contraction. Trials in which the activity of the a-APB exceeded a background noise level of 25 µV were removed and repeated\(^5\); therefore, each participant had the same number of trials in subsequent analysis.

Electromyographic Recording

Pairs of Ag/AgCl electrodes (pregelled, recording area 9 mm × 6 mm, Alpine Biomed ApS, Denmark) were positioned on the skin over the belly of each muscle. The ground electrode was applied on the ulnar styloid process of the affected side. The EMG signals were amplified (1000×) and filtered (20 Hz to 3 kHz) and recorded on a computer (Neur�� MEB-9100; Nihon Kohden Corp, Tokyo, Japan) for offline analysis.

TMS Measurements

Motor-evoked potentials were evoked using TMS (Magstim200, Magstimp, Whitland, Carmarthenshire, UK) through a double-cone coil (110-mm coil diameter). Using a posterior-anterior orientation of the double-cone coil, the optimal stimulating point was found by locating the area that produced the largest and most consistent MEPs in the a-APB; the position of the coil was then marked on the swimming cap worn by the subjects to ensure consistent placement of the coil throughout the experiments. The resting motor threshold was determined as the lowest intensity of TMS output that was required to evoke MEPs of at least 50 µV peak-to-peak amplitude in at least 3 of 5 consecutive trials.\(^6\) In the participants who had no MEP response in the a-APB, we identified the location of the ABP hotspot in the contralesional M1 and the coil was placed on the lesioned M1 mirroring that location (ie, the number of centimeters lateral and anterior to the vertex). Ten stimuli were delivered at an intensity of 1.2 times the resting motor threshold in the rest condition and during the active conditions. The stimulus intensity was set at maximum (ie, 100% stimulator output) for participants in whom an MEP response was not observed. To determine the amplitude of the maximal peripheral motor response (M-max) of the APB, the median nerve was stimulated (1-ms rectangular pulse) with supramaximal intensity using bipolar surface electrodes placed on the ventral side of the wrist (Neur操 MEB-9100; Nihon Kohden Corp, Tokyo, Japan).

Data Analysis

Participants exhibiting an average peak-to-peak MEP amplitude of at least 50 µV after subtraction of background
EMG on the a-APB were defined as MEP present (MEP-APB); the remaining participants were defined as MEP absent (nMEP-APB). Participants with absent MEP then were assigned to 2 subgroups depending on the existence of crossed facilitation: participants who had recordable MEPs during any of the active conditions were defined as having crossed facilitation (nMEP-APBCF) and the remaining participants were defined as having no crossed facilitation (nMEP-APBnCF). In the MEP-APB group, crossed facilitation was identified when the average MEP amplitude during either the APB task or TA task exceeded 2 times the standard deviation of their average MEP amplitude during the rest condition.

The amplitude of the MEP was normalized to the amplitude of M-max. Crossed facilitation in the a-APB was calculated as a change in the MEP amplitude between the active and rest conditions: (active condition −rest condition)/rest condition. The mean prestimulus EMG activity was calculated as the root mean square of the 40-ms prestimulus interval from each condition.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp, Armonk, NY). Nonparametric tests were applied for all the comparisons, because some of the variables did not pass the normality test (Shapiro-Wilk test; \( P > 0.05 \)). Mann-Whitney \( U \) tests were applied to compare the FMA-UE scores between participants with and without recordable MEP responses at rest. A Kruskal-Wallis test with Mann-Whitney \( U \) tests as a post-hoc test was employed to compare FMA-UE scores among the 3 groups (MEP-APBCF, nMEP-APBCF, and nMEP-APBnCF). In addition, the Wilcoxon signed-rank test was used to assess the degree of crossed facilitation between the APB task and the TA task in the MEP-APBCF group. Furthermore, Spearman’s rho correlation analysis was used to examine the relationship between FMA-UE scores and crossed facilitation. Receiver operating characteristic (ROC) analysis was used to determine the FMA-UE score that could most accurately distinguish between participants in whom MEPs could versus could not be evoked, and who did versus did not exhibit crossed facilitation in the a-APB. Cutoff scores were established for the optimal tradeoff between sensitivity and specificity values using the formula: sensitivity + specificity −1. A Friedman’s test was used to examine the prestimulus EMG across conditions. The data are presented as the mean ± standard deviation; the level of significance was set at \( P < 0.05 \). A Bonferroni correction was applied to allow for multiple comparisons.

RESULTS

Characteristics of the MEP Responses of the Participants

There were no significant differences in the FMA-UE scores and MEP responses with respect to the side and type of stroke (Table 1).

Of the 58 participants, 28 exhibited MEPs of the a-APB at rest. All the participants with MEPs present at rest exhibited MEPs in the a-APB with contraction of muscles on the unaffected side (ie, the crossed facilitation). Of the 30 participants with an absent MEP on the a-APB at rest, 7 participants exhibited MEPs in the a-APB with contraction of either APB or TA muscle on the unaffected side; 3 of the 7 had the MEPs only during the TA task and 4 of the 7 had the MEPs during both tasks. Furthermore, there was no significant difference in the degree of crossed facilitation between the APB and TA tasks in the MEP-APBCF group (\( n = 28 \); \( Z = −1.61; P = 0.11 \); Figure 1). There was no effect of condition (APB task vs TA task) on the prestimulus EMG (\( χ^2(2) = 2.70; P = 0.26 \)).

Motor Status and Facilitation of the Lesioned Motor Cortex

Participants with an MEP evoked at rest in the a-APB exhibited higher mean scores on the FMA-UE (\( n = 28 \); FMA-UE, 53.04 ± 2.59) compared with participants with absent MEP (\( n = 30 \); FMA-UE, 19.83 ± 1.60) (\( Z = −6.21; P < 0.001 \); Figure 2A). There was a group effect on FMA-UE (\( H(2) = 41.02; P < 0.001 \)), and post-hoc tests reveal the mean score on the FMA-UE was higher in the MEP-APBCF group (\( n = 28 \)) than in the nMEP-APBCF group (\( n = 7 \)) (\( Z = −3.54; P < 0.001 \)) and nMEP-APBCF groups (\( n = 23 \)) (\( Z = −5.93; P < 0.001 \))(Figure 2B). The mean score on the FMA-UE also was higher in the nMEP-APBCF group than in the nMEP-APBnCF group (\( Z = −2.66; P = 0.008 \))(Figure 2B).

Clinical Correlation and Classification

The FMA-UE scores were significantly correlated with the degree of crossed facilitation during the APB task (\( n = 58 \); \( r = 0.68; P < 0.001 \); Figure 3A) and the TA task (\( n = 58 \); \( r = 0.54; P < 0.001 \); Figure 3B).

Table 1. Demographic Characteristics a

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MEP-APBnCF (n = 23)</th>
<th>nMEP-APBCF (n = 7)</th>
<th>MEP-APBCF (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, male/female</strong></td>
<td>17/6</td>
<td>7/0</td>
<td>19/9</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>59.74 ± 14.56 (39-82)</td>
<td>60.50 ± 15.64 (33-78)</td>
<td>58.29 ± 10.99 (32-81)</td>
</tr>
<tr>
<td><strong>Onset, y</strong></td>
<td>2.21 ± 1.76 (0.5-6.0)</td>
<td>3.45 ± 1.62 (1.0-5.0)</td>
<td>2.78 ± 2.03 (0.5-9.0)</td>
</tr>
<tr>
<td><strong>Type of stroke, ischemic/hemorrhagic</strong></td>
<td>12/11</td>
<td>4/3</td>
<td>17/11</td>
</tr>
<tr>
<td><strong>Hemisphere of lesion, right/left</strong></td>
<td>15/8</td>
<td>18/10</td>
<td></td>
</tr>
<tr>
<td><strong>Fugl-Meyer assessment—upper extremity</strong></td>
<td>18.30 ± 8.95 (8-49)</td>
<td>24.86 ± 6.56 (11-29)</td>
<td>53.04 ± 13.72 (26-65)</td>
</tr>
</tbody>
</table>

Abbreviations: APB, abductor pollicis brevis; MEP, motor-evoked potential; nMEP-APBCF, participants who exhibited no MEPs on the affected limb and no crossed facilitation; nMEP-APBnCF, participants who exhibited crossed facilitation but no MEPs; and MEP-APBCF, participants who exhibited both MEPs on the affected limb and crossed facilitation.

aThe data are presented as the mean ± standard deviation (range) or number.
The results of the ROC analysis revealed that the FMA-UE score was able to classify the presence/absence of MEP in a-APB (Figure 4A). A cutoff point of 29 produced a sensitivity and specificity of 0.89 and 0.93, respectively. Furthermore, the results of the ROC analysis revealed that the FMA-UE score was able to classify the presence/absence of crossed facilitation in a-APB (Figure 4B). A cutoff point of 25 produced a sensitivity and specificity of 0.97 and 0.78, respectively.

**DISCUSSION**

The current study showed that persons with stroke who exhibited MEPs in the affected hand muscle at rest had higher FMA-UE scores compared with those with an absent MEP. In addition, participants both with and without MEPs who exhibited crossed facilitation in the affected hand muscle had higher FMA-UE scores compared with participants without crossed facilitation. Moreover, the FMA-UE scores were positively correlated with the degree of crossed facilitation, which indicates that participants who had better motor function in the upper limb during the chronic stage were able to induce a greater enhancement in corticospinal tract excitability of the affected hand muscle when contracting the muscles on the unaffected limb (Table 1).

The recruitment of M1 ipsilateral to a unilateral movement of either the affected or unaffected hand has been reported as a sign of poor motor recovery after stroke. This finding has been deduced primarily from studies that have used phasic movement as the test stimuli. In healthy adults, a unilateral phasic movement of low force induces an inhibitory effect rather than a facilitatory effect on the neural activation of ipsilateral M1. Therefore, the increase in ipsilateral M1 activation during a unilateral phasic movement in persons with stroke may represent an exaggerated neural response. In contrast, the motor task we used in the present study required a tonic contraction that normally enhances ipsilateral M1 neural activation. Therefore, for tonic movement, crossed

![Figure 1](image1.png)

Figure 1. Task comparison in participants who exhibited both MEPs and crossed facilitation (n = 28) on the abductor pollicis brevis muscle of the affected hand (a-APB). TA, tibialis anterior. The data are presented as the mean ± standard error.

![Figure 2](image2.png)

Figure 2. (A) Comparison of motor function between participants with (MEP-APB; n = 28) and without (nMEP-APB; n = 30) motor evoked potentials on the abductor pollicis brevis muscle of the affected hand (a-APB). (B) Comparisons of motor function among 3 subgroups of participants: nMEP-APB<sub>CF</sub>, participants who did not exhibit either MEPs or crossed facilitation (n = 23); nMEP-APB<sub>CF</sub>, participants who exhibited crossed facilitation but not MEPs (n = 7); and MEP-APB<sub>CF</sub>, participants who exhibited both MEPs and crossed facilitation (n = 28). The data are presented as the mean ± standard error. *P < 0.05.
facilitation to represent favorable preservation of motor function of the affected arm. 

The degree of crossed facilitation would not be considered abnormal neural activation in persons with stroke. For this reason, we interpret this crossed facilitation to represent favorable preservation of motor cortical pathways, as the degree of crossed facilitation was correlated with the level of motor function. 

There are several candidates that may mediate crossed facilitation. For example, the uncrossed corticofugal fibers ipsilateral to the lesioned M1 might contribute to this facilitation. However, it has been shown that the recruitment of ipsilateral pathways does not seem to lead to a greater degree of functional recovery.28,29 Other motor pathways relevant to the modulation of crossed facilitation are the transcallosal pathways, which connect the bilateral motor cortices. Transcranial magnetic stimulation can be used to study this pathway using paired-pulse protocols to assess interhemispheric inhibition. Previous studies have demonstrated that interhemispheric inhibition from contralateral to ipsilateral M1 is associated with changes in the MEP amplitude during unilateral movement in healthy subjects.30,31 Given that this transcallosal inhibition could modulate the level of crossed facilitation, abnormal inhibitory activation from the contralesioned M1 to lesioned M1 during voluntary movements could adversely influence motor recovery.32-34 Participants in our study who did not exhibit crossed facilitation may have poor motor function because of impaired modulation of the transcallosal pathways. Furthermore, a recent study has reported that compared with healthy controls, participants with stroke exhibit less increase in inhibition from the contralesioned to lesioned M1 from their active to resting M1 during a unilateral tonic contraction, and the degree of altered inhibition was correlated with the motor function of the affected arm.35 The involvement of spinal circuits in the facilitation of the lesioned might need to be considered. However, the exaggerated spinal reflexes are related to poor motor outcome, and therefore this explanation seems unlikely.36,37

The degree of integrity of the corticospinal tract on the lesioned side corresponds to the prognosis of motor recovery after a stroke.37-40 Our results demonstrate that participants with an absent MEP at rest who did not exhibit enhanced excitability of the corticospinal tract via the contraction of the unaffected muscles had the most severe motor impairment. In addition, the cutoff point at which the FMA-UE score classified the presence/absence of crossed facilitation was 25; participants with scores at or below these cut-off were constrained mostly in movements that involve abnormal synergistic movements (eg, flexor and extensor synergistic movements of the upper limb). As synergistic movements during the chronic stage of a stroke indicate poor motor recovery,41,42 this is consistent with the idea that poor motor outcomes indicate greater damage to the motor neural pathways.

The degree of crossed facilitation is muscle-specific. Results from healthy subjects have demonstrated that contraction performed by the homologous muscle enhances corticospinal excitability to a larger extent than does contractions performed by a different muscle on the opposite side.19,31,43,44 In the current study, visual inspection of the MEP data suggested that the size of the a-APB MEPs evoked by the APB task may have been greater than that evoked by the TA task in the MEP-AFB group. If this impression is correct, then this would support previous findings that have demonstrated a reduction in the linear relationship between the contraction strength and the degree of crossed facilitation after a stroke.12 Therefore, this impaired response in the lesioned M1 after stroke in terms of a dependency on the motor task may be due to general alterations within the motor neural circuits.

A recent review article has reported that the severity of motor deficit after stroke is determined by the lesion of the corticospinal tract rather than the size or location of the cerebral lesion,3 which may correspond to our findings that the FMA-UE scores were significantly different between participants with and without MEP responses but similar between participants with ischemic and hemorrhagic stroke. Furthermore, given that we did not limit the stroke type and location (eg, cortical vs subcortical) in our study, the present results represent a general response of the lesioned M1 during a tonic contraction on the unaffected side in individuals poststroke. Given that crossed facilitation may contribute to interlimb coordination.

Figure 3. Correlations between the scores on the FMA-UE and the level of crossed facilitation on the abductor pollicis brevis of the affected hand (a-APB) during contractions of the (A) thumb abductor (APB task) and (B) ankle dorsiflexor (TA task) of the unaffected limbs. All participants (n = 58) were included in the analysis.
and enhancement of motor performance after repeated training, we suggest that persons with an FMA-UE score higher than 25 who exhibit crossed facilitation may achieve greater motor improvements after intervention than persons with an FMA-UE score less than 25 who do not exhibit crossed facilitation.

CONCLUSIONS

Our results demonstrate that in some individuals with stroke the motor output in the affected hand muscle can be enhanced by a tonic contraction of the muscles on the unaffected limb. However, this crossed facilitation was not observed in all participants. We found that the degree of crossed facilitation in the affected hand muscle was correlated with the level of motor function of the affected upper limb, and the presence/absence of crossed facilitation could be classified by the FMA-UE score. The present results have clinical relevance to poststroke rehabilitation as they indicate that tonic muscle contraction of the unaffected hand or foot can enhance motor output of the stroke-affected hand.

ACKNOWLEDGMENTS

We thank those individuals who participated in this study.

REFERENCES

guidelines for the Fugl-Meyer test, action research arm test and box and
cortex excitability during ipsilateral hand muscle activation in humans. 